

Building Active Atlas for Mouse Brainstem

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Abstract. We propose a semi-supervised system for generating a reference atlas from histology image series of the mouse brainstem. The atlas contains the mean and variance of the positions and shapes of nine anatomical landmarks. By learning landmark classifiers, the system registers new data to the atlas. Registered data further improve the generalizability of the classifiers.

Keywords: landmark detection, atlas generation, mouse brain, registration, automated annotation

1 Overview

With the advance of genetic labeling and high-throughput imaging techniques, there is an increasing need for brain atlases that characterize gene expression by statistical summarization of genetic expression information in a large number of subjects.

The common workflow for building an atlas is to first generate an anatomical reference model by “averaging” many brains and then register the gene expression patterns to this model.

This allows one to computationally quantify the variance between individuals, and allows one to identify the anatomical identities of regions of certain gene expressions.

Existing atlases of the mouse brain include Paxinos, Waxholm Space [4], and the more recent Allen Reference Atlas [3] and its successors, on top of which gene expression data [6, 7] as well as connectivity information [8] are mapped. The latest version of their common coordinate framework [1] is generated by deformably averaging two-photon microscopy images and manually demarcating structures with the help of immunohistochemistry data and genetic labeling data. Atlases for smaller organisms such as fruit flies [2, 9] and zebrafish [10, 11] are mostly based on volumetric images acquired by confocal microscopy. For registration, the BrainAligner program [9] relies on matching high-curvature points, and the ViBE-Z project [11] used trained classifiers to detect predefined 3D landmarks.

These atlases are not updateable from new data, and do not provide means that facilitate the registration of new data.

This paper proposes a machine-learning based method that generates an anatomical reference model from Nissl-stained cryo-section images.

In addition to describing the statistics of position and shape of anatomical structures, the model also include landmark detectors. These detectors are texture classifiers trained in a semi-supervised fashion to detect regions with salient texture that can serve as registration landmarks, such as nuclei and tracts. Because these detectors allows our

system to actively detect landmarks on new data for registration, instead of being a mere registration template; and also because these detectors can update themselves from new data, we refer to this system as an “active atlas”.

2 Methodology

Registration to the atlas is based on landmark probability maps generated by the classifiers.

An M -way classifier detects landmarks on each image, assigning a probability vector to each pixel. Intra-stack registration is performed for each stack separately based on intensity. Assuming constant section thickness and the sections being parallel, a volume can be reconstructed for each stack, in which every voxel has a probability vector.

Given a stack of section images, the *elastix* program [5] is used to find rigid transformations that align every pair of consecutive sections, by maximizing the normalized correlation of image intensity. These transformations are then composed, bringing the whole stack into a rough alignment. Because the tape-transfer system used to process these sections preserves the tissues very well, 3-parameter rigid transforms are sufficient for this stage of registration.

For each image in the stack, a M -way classifier assigns a landmark probability vector to each pixel. The result is a set of score maps S_l , one for each landmark.

We then register the test volume to the atlas. A 3D rigid transform is sought that maximizes the same-class overlap score between the test volume and the atlas. The score is defined as:

$$M(T) = \sum_l \sum_{p \in V_l} S_l[T(p)],$$

where T is the transformation that maps voxels from the atlas to the test volume, l indexes the landmark labels, V_l is the set of voxels in the atlas with label l , S_l is the score map for label l .

The optimal parameters are found using a coarse-to-fine grid search, followed by gradient descent that moves the solution towards the maxima.

References

1. Technical white paper: Allen mouse common coordinate framework. Tech. rep. (2015) [1](#)
2. Chiang, A.S., Lin, C.Y., Chuang, C.C., Chang, H.M., Hsieh, C.H., Yeh, C.W., Shih, C.T., Wu, J.J., Wang, G.T., Chen, Y.C., et al.: Three-dimensional reconstruction of brain-wide wiring networks in drosophila at single-cell resolution. *Current Biology* 21(1), 1–11 (2011) [1](#)
3. Dong, H.: Allen Reference Atlas: a digital color brain atlas of the C57BL/6J male mouse. John Wiley & Sons (2008) [1](#)
4. Johnson, G.A., Badea, A., Brandenburg, J., Cofer, G., Fubara, B., Liu, S., Nissanov, J.: Waxholm space: an image-based reference for coordinating mouse brain research. *Neuroimage* 53(2), 365–372 (2010) [1](#)
5. Klein, S., Staring, M., Murphy, K., Viergever, M.A., Pluim, J.P.: Elastix: a toolbox for intensity-based medical image registration. *Medical Imaging, IEEE Transactions on* 29(1), 196–205 (2010) [2](#)

6. Lein, E.S., Hawrylycz, M.J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., Boe, A.F., Boguski, M.S., Brockway, K.S., Byrnes, E.J., et al.: Genome-wide atlas of gene expression in the adult mouse brain. *Nature* 445(7124), 168–176 (2007) [1](#)
7. Ng, L., Bernard, A., Lau, C., Overly, C.C., Dong, H.W., Kuan, C., Pathak, S., Sunkin, S.M., Dang, C., Bohland, J.W., et al.: An anatomic gene expression atlas of the adult mouse brain. *Nature neuroscience* 12(3), 356–362 (2009) [1](#)
8. Oh, S.W., Harris, J.A., Ng, L., Winslow, B., Cain, N., Mihalas, S., Wang, Q., Lau, C., Kuan, L., Henry, A.M., et al.: A mesoscale connectome of the mouse brain. *Nature* 508(7495), 207–214 (2014) [1](#)
9. Peng, H., Chung, P., Long, F., Qu, L., Jenett, A., Seeds, A.M., Myers, E.W., Simpson, J.H.: Brainaligner: 3d registration atlases of drosophila brains. *Nature methods* 8(6), 493–498 (2011) [1](#)
10. Randlett, O., Wee, C.L., Naumann, E.A., Nnaemeka, O., Schoppik, D., Fitzgerald, J.E., Portugues, R., Lacoste, A.M., Riegler, C., Engert, F., et al.: Whole-brain activity mapping onto a zebrafish brain atlas. *Nature methods* 12(11), 1039–1046 (2015) [1](#)
11. Ronneberger, O., Liu, K., Rath, M., Rueß, D., Mueller, T., Skibbe, H., Drayer, B., Schmidt, T., Filippi, A., Nitschke, R., et al.: Vibe-z: a framework for 3d virtual colocalization analysis in zebrafish larval brains. *Nature Methods* 9(7), 735–742 (2012) [1](#)